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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,915	08/15/2001	Ashley J. Birkett	ICC-102.2US 81175	2278

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EXAMINER	
PENG, BO	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,915	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-17,19-33,35-38 and 42-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-17,19-33,35-38 and 42-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bo Peng, Art Unit 1648.

2. This Office Action is in response to the amendment filed September 12, 2005. Claims 1-9, 12-17, 19-33, 35-38 and 42-78 are pending, and are under consideration in this Office action.

3. The rejection of claims 1, 18, 42, 63, 75 and 78 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, **is withdrawn** in view of Applicant's argument.

4. The rejection of claims 1-9, 12-17, 19-33, 35-38 and 42-78 under 35 U.S.C. § 112, first paragraph for lacking enablement, **is maintained**.

5. Claims 1-9, 12-17, 19-33, 35-38 and 42-78 are drawn to HBc chimer molecules containing no more than 20%, 10% or 5% conservatively substituted amino acids of HBc sequence.

6. Applicant argues that the articles cited in the previous Office action are irrelevant to the present claims as the articles teach nothing about the relationship between the structure and the function of HBc molecule. Moreover, the HBc protein itself has little biological activity, such as receptor binding, etc., in the use disclosed in this application other than as a carrier of an

immunogen. Therefore, no much function of HBc would be affected by the substitution of 5-20% other amino acids.

7. Applicant's arguments have been considered but not found persuasive for following reasons: The articles cited in the previous Office action prove a basic rule in the protein art that manipulating a protein structure can affect its biological function. This basic rule also applys to an HBc protein. As a carrier, an HBc molecule in this application has its unique biological activity of viral particle assembly and RNA packaging. Like other proteins, the ability of an HBc molecule to form viral particles can be affected by changes in its structure. As shown in the instant specification (Example 6), with or without one cysteine at the C-terminus of HBcΔ can affect the stability of the HBcΔ viral particle. Thus, Applicant has not provided any reason why one would not expect this rule would not have general applicability and would not apply to an HBc protein.

8. Since HBc variants differ in their sequences and structural requirements for their capsid formation, one skilled in the art would need specific directions on how to manipulate HBc variants having 80% similarity to HBc to display epitopes and also form stable particles. There is no reference in the art indicating that the current knowledge of making a virus-like particles (VPL) using an HBc can be readily applied to any sequences that are more than 80% similarity to an HBc protein, and have reasonable expectation of success that such undefined sequences can form a stable VPL. The instant specification has not disclosed any HBc-like sequence with 5- 20% substitutions of other amino acids that can form the a stable HBc-like chimer. Thus the specification fails to provide these directions for making VLP using undefined HBc variants.

9. Based on the lack of guidance and working examples and unpredictable nature of the art, one skilled in the art would have to do an undue amount of experimentation to test large amounts of HBc variants with undefined sequences encompassed by the claims to see if they meet the function limitation of the claims to form stable virus like particles. Therefore one skilled in the art cannot practice the claimed invention without undue experimentation.

10. The rejection of claims 1-8, 18, 27, 28, 32, 33, 42, 63 and 75 under 35 U.S.C 102(b) as being anticipated by Ireland (US 5,990,085) **is withdrawn** in view of Applicant's argument.

11. The rejection of claims 1-9, 12-33, 35-38 and 42-78 under 35 U.S.C. 103(a), as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al (1997), **is maintained**.

12. Applicant argues that the rejection should be withdrawn because (1) Pumpens' constructs have no stabilization at the C-terminus of a HBcΔ, and Pumpens does not teach a heterologous linker in his constructs; (2) Zlotnick's reference does not apply to the instant claims because Zlotnick has neither an insert epitope in his construct, nor a suggestion of where to put one; and (3) "The combining of the two disclosure is rather the result of a hindsight expedition looking for bits and pieces of unrelated art that could be put together to seem to make up a whole but have no conceptual glue to keep itself together" (Remarks, paragraph 3, p. 29).

13. Applicant's arguments have been considered but are found not persuasive for the following reasons:

14. First at all, in response to Applicant's argument (3) first, both Pumpens and Zlotnick are not "unrelated art" as suggested by Applicant in the Remarks. Instead, both references are

relevant to the instant invention as they are cited by Applicant in "BACKGROUND OF THE INVENTION" of the instant application. Therefore, they do have "conceptual glue to keep itself together". Both Pumpens and Zlotnick, along with other reference cited in the specification, have provided the knowledge generally available to one of ordinary skill in the art at the time the instant invention as made, and would lead that individual to combine the relevant teachings of the references.

15. In response Applicant argument (1) that Pumpens' constructs have no stabilization at the C-terminus of a truncated molecule, and Pumpens does not teach a heterologous linker in his constructs, Pumpens does not teach stabilization at C-terminus of a truncated HBc molecule, but Zlotnick teaches the addition of a single heterologous Cys at a truncated C-terminal of HBV can stabilize the virus capsid (see discussion below).

16. Regarding the linkers discussed by Pumpers, Applicant argues that those linkers are DNA polylinker sequences, not a protein. Unfortunately, the Examiner has found that it is Applicant, rather than the Office action, that has mischaracterized Pumpens' short polylinkers. Pumpens teaches: "Another specific approach involves the insertion of short polylinkers which code for minimal well-characterized epitopes, so-called immunological markers, e.g. DPAF, necessary and sufficient for recognition by murine monoclonal antibody MA18/7 (Pumpens, paragraph 4, line 6-10, left column, p. 69; emphasis added). Clearly, Pumpens is talking about an epitope that can be recognized by an antibody MA18/7. Consistently, in Fig. 2 of Borisova's paper, which was cited as a reference in Pumpens discussion, the epitope polylinker, illustrated in both nucleotide acid and amino acid sequences, is inserted at positions 78 and 144 of an HBcΔ molecule (Borisova, 1996, Intervirology Vol. 39, pp 16-22). The figure of legend specifically

points out "Polylinker inserted as nucleotide and corresponding peptide sequences. 'Immunological markers' presented by HBV pre-S MA18/7-recognized epitope is highlighted". After all, Pumpens' polylinker is a specific epitope, not only DNA polylinker as characterized by Applicant. Therefore, the Office action has not mischaracterized the reference. The polylinkers described by Pumpens and evidenced by Borisova (1996) meet the limitation of "a heterologous linker residue" of the instant claims. Nevertheless, as pointed out in the previous Office action, claims 1, 18, 51 and 63 require EITHER a heterologous epitope OR a linker residue for a heterologous epitope. Either way, Pumpens provides the necessary structure.

17. Applicant's argument (2) that Zlotnick has neither an insert epitope in his construct, nor a suggestion of where to put one is not convincing. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

18. Zlotnick's study is related to HBV assembly, which has provided general knowledge that would lead one of ordinary skill in the art to combine the relevant teachings of the references. Specifically, Zlotnick has studied the encapsidation and organization of a HBV pregenome by investigating the determinant of HBV capsid assembly. Zlotnick teaches that the protamine domain (residues 150-183) is required for packaging RNA and that deletion of this region results in the generation of virus capsids free of RNA and that deletion of this region results in the generation of virus capsids free of RNA encapsidation (abstract; pg. 9556, col.1; pg. 9560, col.

2).

19. Zlotnick also teaches that the addition of a single heterologous Cys at a truncated C-terminal of HBV can stabilize the virus capsid after deletion of its protamine domain 150-183. (See Capsids assembled from Cpg. 9558, col. 6). To illustrate this, Zlotnick has created constructs Cp*149 and Cp*150 which contain HBc having a deleted C-terminal. He has replaced three native internal Cys by three Ala in the constructs Cp*149 and Cp*150, since Ala is a simplest amino acid residue and has minimal effect on the formation of higher protein structure. In addition, Zlotnick has introduced a single heterologous Cys at the truncated C-terminal of Cp*150. Zlotnick has shown that the Cp*150 construct that contained no internal Cys and had a C-terminal Cys is more stable than the Cys-free construct Cp*149, suggesting that disulfide bond formation by Cp*150 can promote capsid assemble (Results and Discussion, paragraph 1 and 2, p. 9558).

20. Thus, Zlotnick has provided the knowledge of minimal determinant of HBV capsid assembly, which is important for the art of basic and applied HBV virology, because "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In the instant case, one of ordinary skill in the art would apply this general knowledge of HBV assembly to the construction of HBc chimer.

21. As discussed in the previous Office action, it is known in art that one of the potential problems with full-length HBc core protein molecules is that the C-terminal sequence, including the protamine region, is responsible for the packaging of nucleic acid, and, moreover, when one

includes this region in a chimera one runs the risk of inadvertent transfer of endogenous nucleic acid from the host cell (See Ulrich, et al., 1998, pg. 163; cited by applicant as A108). Deletion of protamine domain results in virus capsids free of RNA encapsidation (abstract; pg. 9556, col.1; pg. 9560, col. 2).

22. One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining the various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

23. One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

24. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. The Applicant has not provided any compelling reason or evidence to overcome the rejection under 35 U.S.C. §103.

Remarks

25. No claims are allowed. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

26. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Bo Peng, Ph.D.
June 26, 2006

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